REMARKS

Reconsideration and allowance of the subject application are respectively requested.

Claims 14-17 are pending in this application. Claims 1-13 were previously cancelled and claims 18-23 are now cancelled. Claims 14-17 are currently amended.

In response to the Examiner's restriction of the claims and examination of Group I claims 14-17, the withdrawn Group II claims 18-23 have been cancelled. All of the claims withdrawn as reading on a non-elected invention in this application, have been cancelled so that the applicants may file one of more divisional applications.

The specification has been amended as requested by the Examiner to correct trademark format, insert SEQ ID NOS where missing and appropriately refer to figures in the Brief Description of Drawings section.

The Abstract has been amended to insert SEQ ID NOS where missing.

The Title has been amended to more clearly indicate the claimed invention.

At page 3, first paragraph of the Office Action, the Examiner points out that the Brief Description of Drawings, regarding Figure 1, and the Abstract refer to sequences but do not disclose SEQ ID NOS. The Brief Description of Drawings, regarding Figure 1 has been accordingly amended by inserting the appropriate SEQ ID NOS.

Additionally, the Abstract has been amended by insertion of the appropriate SEQ ID NOS.

The applicants submit that the present application conforms with the Sequence Rules as set forth in 37 CFR 1.821-1.825.

With further respect to the drawings of record in this application, the applicants note that the Examiner has not completed item 10, page 1 of the present Office Action nor the prior Office Action dated October 4, 2004. Item 10 is a part of the "Application Papers" and confirms acceptance of the drawings. The applicants respectfully ask the Examiner to confirm acceptance of the drawings.

In response to the Examiner's comments about the priority date of the present application, the applicants point out that the present application claims priority based on Japanese patent application No. 2000-117394 which was filed on April 19, 2000. This information is indicated in WO 01/79298. For the reference of the Examiner, a copy of the relevant page of WO01/79298 is attached to this Amendment. Acknowledgement by the Examiner is respectfully requested.

In response to the Examiner's comments at page 3, section 4 of the Action, about correct trademark format and correct reference to figures, the applicants have reviewed the specification and corrected trademark format where necessary. The applicants have also amended the description of Figures 1-5 in the Brief Description of the Drawings to properly refer to the figures by inserting "A-B" as suggested by the Examiner. Accordingly, the applicants submit the present specification is in proper form.

In response to the Examiner's objection to the title, the title has been replaced, as shown above, with a new title that more clearly indicates the claimed invention. The applicants submit that the amended title is sufficiently descriptive and this objection should be withdrawn.

In response to the rejection of claims 14-17 under 35 USC 112, first paragraph, at page 3, section 7 of the Action, the applicants submit that the claims 14-17, as amended above, overcome this rejection. For example, claim 14 has been amended to recite that the claimed recombinant antibody has at least 6 amino acid sequences as its complementarity-determining regions (CDRs). Further, claims 15 and 16 were in part amended by deleting the phrase "or an amino acid sequence derived from said amino acid sequence by deletion, addition ... represented by SEQ ID NOS: 1 to 3 or its fragment."

Accordingly, the applicants submit that all presently considered claims are fully allowable under Section 112, first paragraph.

With respect to sections 8 and 9, at page 5 of the Action, and in response to the Examiner's objection to claims 14-17 for having awkward language and rejection and rejection of claims 14-17 under 35 USC 112, Second paragraph, claims 14-17 have been amended as shown above. Claims 14-17 have been relevantly amended with regard to the following terms: "antibody against" to "antibody that binds"; "H chain" to "Heavy chain"; "L chain" to "Light chain"; and "or its fragment" to "or a fragment of said recombinant antibody."

The applicants submit that all presently considered claims are fully allowable under Section 112, Second paragraph.

The applicants respectfully traverse the rejection of claims 14-17 under 35 USC 102(b) in view of Nagahira et al. This reference does not anticipate the presently claimed invention or make it obvious.

The present invention is directed to an antibody comprising 6 specific amino acid sequences (SEQ NOS: 1-6) derived from CDRs of H-chain and L-chain of anti-

TNFα antibody 3B10. The amino acid sequences are important features of the presently claimed invention.

In contrast, Nagahira et al. fails to disclose the amino acid sequences of CDRs of the anti TNFα antibody 3B10, which correspond to SEQ Nos. 1-6 of the presently claimed invention. For example, Figure 2 of Nagahira fails to disclose the amino acid sequences of the CDRs. For the Examiner's convenience, a copy of Nagahira Figure 2 is attached to this Amendment, wherein the relevant parts are indicated with a black felt pen.

Please note that the disclosure of Nagahira focuses on framework regions, which are the regions other than CDR. This is clear from the abstract of Nagahira which describes that "Using a molecular model of mouse 3B10, framework residues affecting the CDR conformation were identified."

In general, it is known that CDR is especially variable in its variable regions, and contributes to the wide spread of variation of variable regions. Further, it is also known that CDRs determine the specificity of an antibody against an antigen. On the other hand, framework regions are not considered to determine specificity of an antibody. Thus, amino acid sequences of framework regions are not considered by those of ordinary skill in the art to provide information sufficient and suitable to specify an antibody.

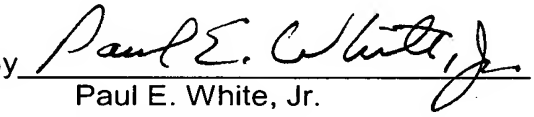
Taking this technical knowledge into account, since Nagahira fails to specify the CDRs of 3B10 antibody, the disclosure of Nagahira cannot substantiate the allegation in the Office Action that Nagahira teaches the same or nearly the same humanization of the same neutralizing anti-human TNFα 3B10 antibody. The presently claimed invention is thus clearly novel in view of Nagahira et al.

Further, since Nagahira fails to disclose the sequence information for CDRs of 3B10, it is difficult for those skilled in the art to practice the present invention of an antibody which comprises CDRs of the 3B10 antibody, based on the disclosure of Nagahira. Thus, Nagahira does not make the presently claimed invention to be obviousness.

Accordingly, the presently claimed invention is no where disclosed, suggested or made obvious by the teachings of Nagahira et al. The presently claimed invention is not only allowable under Section 102(b) but is also allowable under Section 103(a) in view of the cited art.

Respectfully Submitted,

Manelli Denison & Selter, PLLC

By 

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RELEVANT PAGE OF PRIORITY APPLICATION SHOWING PRIORITY DATA

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[続葉有]

(54) Title: NOVEL RECOMBINANT ANTIBODIES, AMINO ACID SEQUENCES OF CDRS THEREOF AND GENES ENCODING THE SAME

(54) 発明の名称: 新規組換え型抗体とそのCDRのアミノ酸配列およびそれをコードする遺伝子

(A) H鎖 H CHAIN

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                          1                   2                   3
        1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0
3B10    Q V K L L E S G P E L K K P G E T V K I S C K A S G Y T F T
HBS-1   Q V Q L L E S G G G V V Q P G R S L R L S C A A S G F T F S

                          4                   5
        1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 a 3 4 5 6 7 8 9
3B10    N Y G M N W V K Q A P G K G L K W M G W I N T Y T G E P T Y
HBS-1   S N S M H W V R Q A P G K G L E W V A V I L Y D G N H K F Y

        6                   7                   8
        0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 a b c 3 4 5 6
3B10    A D D F K G R F A F S L E T S A S T A Y L Q I N N L K N E D
HBS-1   A D S V K G R F T I S R D N S K N T L Y L E V K S L Q T E D

                                  1                   1
              9                   0                   1
        7 8 9 0 1 2 3 4 5 6 7 8 9 0 a b c 1 2 3 4 5 6 7 8 9 0 1 2 3
3B10    M A T Y F C A R Y D Y D G F       D Y W G Q G T T V T V S S
HBS-1   T G V Y Y C I R D Q T Y G V H R F D S W G Q G T L V T V S S
```

(B) L鎖 L CHAIN

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                          1                   2                   3
        1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0
3B10    D V E L T Q S P A I M S A S L G E R V T M T C T A S S S V S
HBS-1   D V Q M T Q S P S A M A A S V G D R V T I T C R A S Q G I G

                          4                   5
        1 2 a 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9
3B10    F S Y L H W Y Q Q K P G S S P K L W I Y S T S N L A S G V P
HBS-1   N Y   L V W F Q Q K P G K V P K R L I Y A A S S L Q S G V P

        6                   7                   8
        0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9
3B10    A R F S G S G S G T S Y S L T I S S M E A E D A A T Y Y C H
HBS-1   S R F S G S G S G T E F T L T I S S L Q P E D F A T Y Y C L

                          1
        9                 0
        0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7
3B10    Q Y L R S P Y T F G G G T K L E I K
HBS-1   H H N N Y P L S F G G G T K V E I K
```

(57) Abstract: An H chain polypeptide or its fragment of a recombinant antibody against human TNFα having at least one of the following amino acid sequences: a) as CDR-H1 Gly-Tyr-Thr-Phe-Thr-Asn-Tyr-Gly-Met-Asn; b) as CDR-H2 Trp-Ile-Asn-Thr-Tyr-Thr-Gly-Glu-Pro-Thr-Tyr-Ala-Asp- Asp-Phe-Lys-Gly; and c) as CDR-H3 Tyr-Asp-Tyr-Asp-Gly-Phe-Asp-Tyr; an L chain polypeptide of a recombinant antibody against human TNFa having at least one of the following amino acid sequences: a') as CDR-L1 Thr-Ala-Ser-Ser-Ser-Val-Ser-Phe-Ser-Tyr-Leu-His; b') as CDR-L2 Tyr-Ser-Thr-Ser-Asn-Leu-Ala-Ser; and c') as CDR-L3 His-Gln-Tyr-Leu-Arg-Ser-Pro-Tyr-Thr; and humanized antibodies against human TNFα or fragments thereof which comprise the above-described H chain polypeptide or its fragment and the above-described L chain polypeptide. Also, a process for producing a humanized anti-TNFα antibody by transforming host cells with an expression vector having a gene encoding the above antibody, etc. is disclosed.

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[続葉有]

MARKED FIGURE 2 OF CITED REFERENCE NAGAHIRA ET AL.

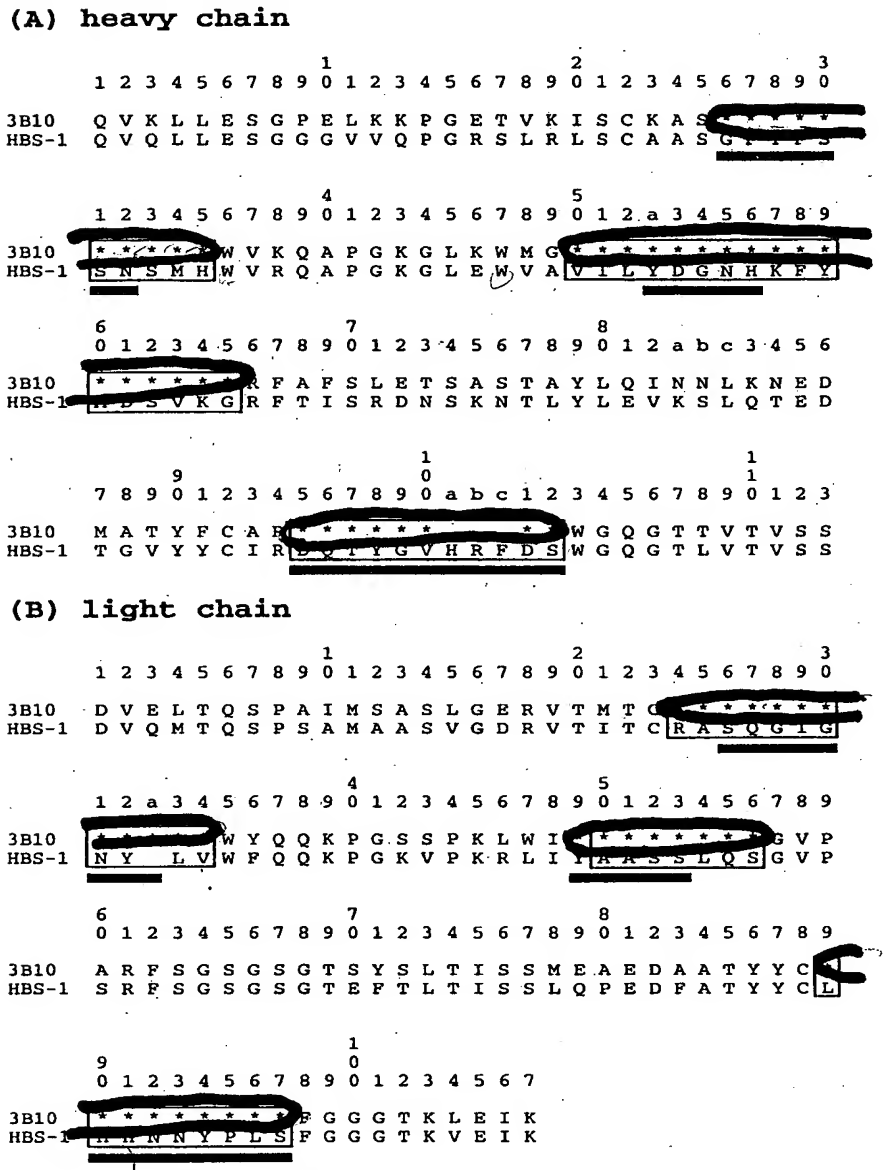

Fig. 2. Amino acid sequences of 3B10 and HBS-1 variable regions. Amino acids (in one-letter notation) are numbered according to Kabat et al. (1991). The CDR residues by sequence (Kabat et al., 1991) and structural (Chothia and Lesk, 1987) definitions are underlined and boxed, respectively. In constructing humanized antibody, the residues involved in at least either of the definitions were grafted as the CDR residues. The CDR residues of 3B10 have been removed on account of patent application. (A) Heavy chain. (B) Light chain.

4–5 Å distance from the CDRs (Fig. 3), indicating that the residues also affect the CDR conformation. The properties of three surface residues near the CDRs (L3, H3 and H46) of 3B10 are distinct from those of HBS-1, because they could influence the CDR structure by electrostatic interaction. For these reasons, we constructed additional five versions of the antibodies derived from h3B10-1, h3B10-2, -3, -4, -6 and -7, in which any of the five residues, H3, H46, H78, L3 and L47, was replaced with its corre-